Antiepileptic drugs

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Epilepsy

DEF: Chronic disorder characterized by recurrent seizures due to abnormal discharge of cerebral neurons

Types:

Cellular Mechanisms of Seizure Generation

- **Excitation (too much)**
  - Ionic-inward Na^{+}, Ca^{++} currents
  - Neurotransmitter: glutamate, aspartate

- **Inhibition (too little)**
  - Ionic-inward Cl; outward K^{+} currents
  - Neurotransmitter: GABA

Mechanism of action of antiepileptic drugs

Reduction of cell membrane permeability to sodium

e.g.
phenytoin, carbamazepine, valproate & lamotrigine

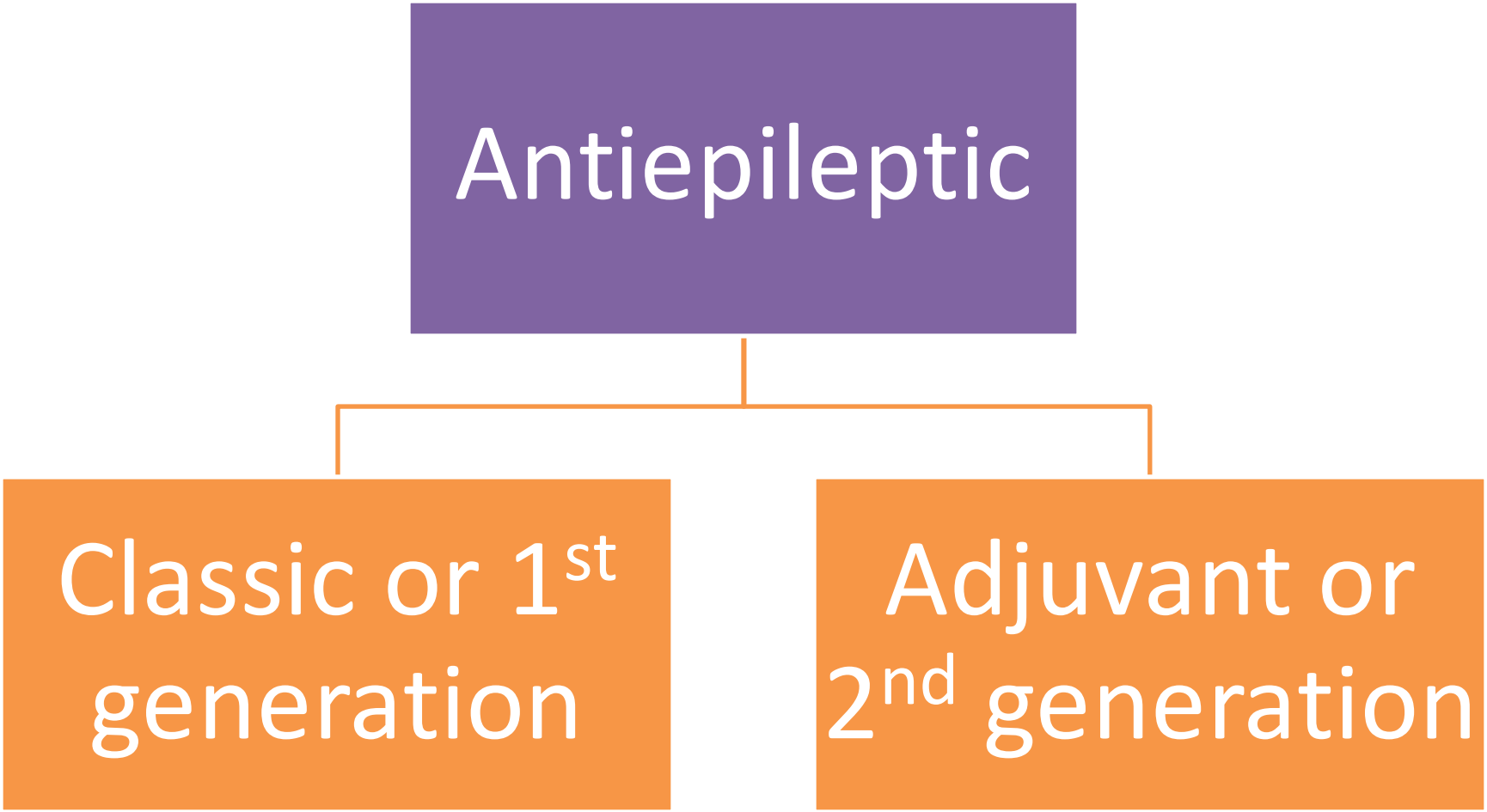
Block of voltage-dependent T-Calcium channels

e.g.
ethosuximide, valproate

Modifying neurotransmitters

A- Enhancement of GABA mediated synaptic inhibition
e.g.
barbiturates, benzodiazepines, vigabatrin & valproate.

B. Decreased excitatory amino acid function
e.g.
felbamate and toprimate



Due to high toxicities of most antiepileptic drugs, monotherapy is preferred and only used Only add on therapy in unresponsive cases or refractory epilepsy

I- Phenytoin and Fosphentoin

Pharmacokinetics:

A: Oral absorption is complete.

D: pass blood brain barrier and placenta

About 90% bound to plasma protein.

- T1/2 = 12-36 hours.

M: It is hydroxylated in the liver and this needs folic acid as cofactor THEN glucuronation to final metabolites

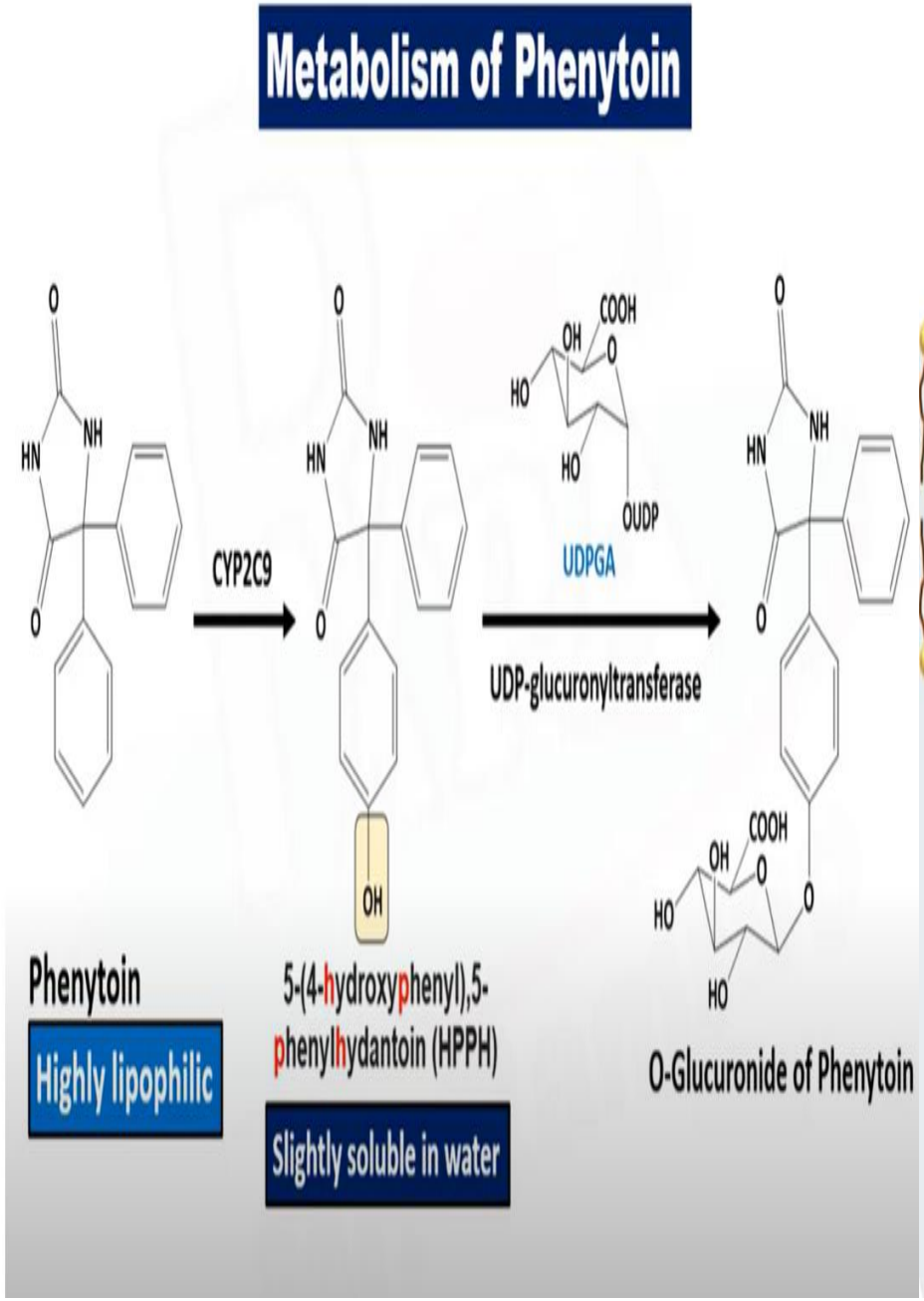
E: Elimination follows saturable kinetics.

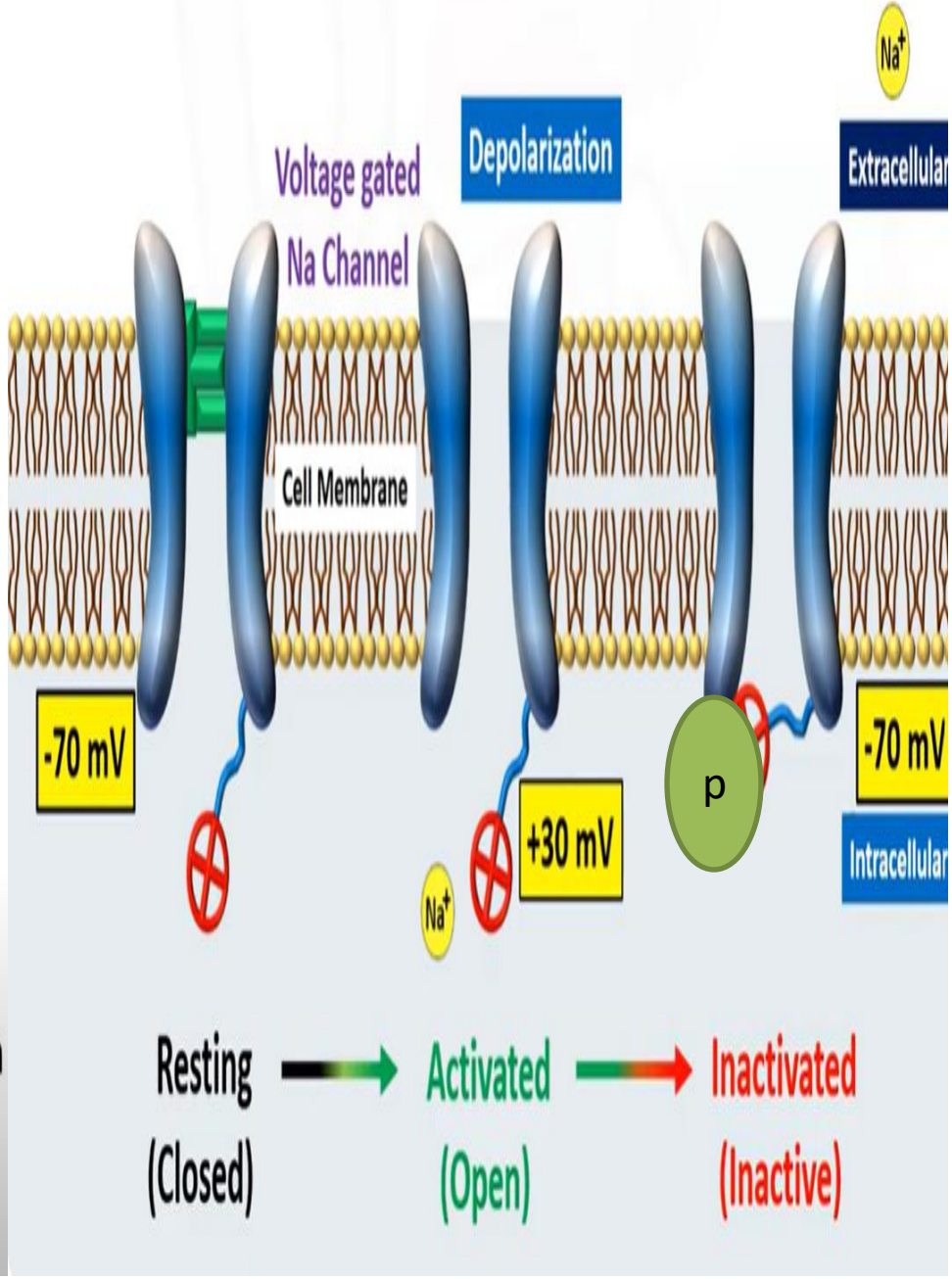
NOTE: Fosphenytoin: prodrug (water soluble) of phenytoin, available for parentral use in status epilepticus (i.v or i.m).

Mechanism of action

It blocks voltage-gated Na+ channels.

At higher concentrations. It can block voltage-dependent Ca++ channels & interferes with release of neurotransmitters.


Metabolism of Phenytoin
CYP2C9
UDPGA
UDP-glucuronyltransferase
Phenytoin
Highly lipophilic
5-(4-hydroxyphenyl),5-phenylhydantoin (HPPH)
Slightly soluble in water
O-Glucuronide of Phenytoin


Voltage gated
Na Channel
Depolarization
Extracellular
Cell Membrane
-70 mV
+30 mV
p
-70 mV
Intracellular
Resting
(Closed)
Activated
(Open)
Inactivated
(Inactive)

Pharmacological actions:

1.Antiepileptic: it has selective antiepileptic action without causing CNS depression.

2 Antiarrhythmic: it depresses automaticity, excitability & increased conduction velocity, so abolish reentry arrhythmias.

Therapeutic uses:

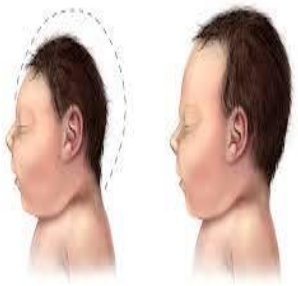
1. Antiepileptic:

A. focal seizures

B. Status epilepticus (Fosphenytoin).

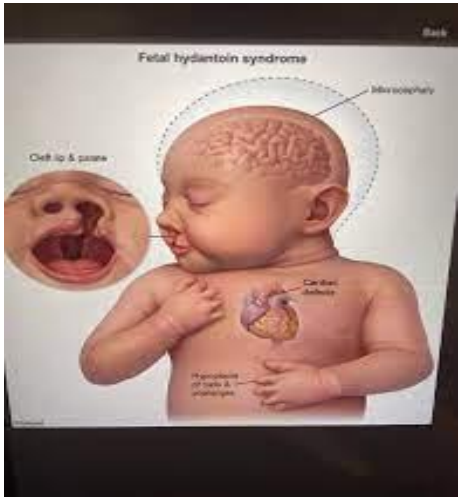
2. Ventricular arrhythmia.

Side effects



1. C.N.S: Nystagmus, diplopia, ataxia & vertigo.
2. Liver: enzyme inducer
3. Blood: Megaloblastic anemia

it interferes with folate absorption and/or metabolism.



4- Teratogenicity:

- If taken in the first trimester, cleft palate and hare lip (fetal hydantoin syndrome).
- Cardiac septal defect
- Hypoprothrombinemia of the baby, if taken before labor.
- Neural tube defect (spina bifida)

5. Gingival hyperplasia.

6. Hypersensitivity reactions such as rash, fever, and lymphadenopathy.

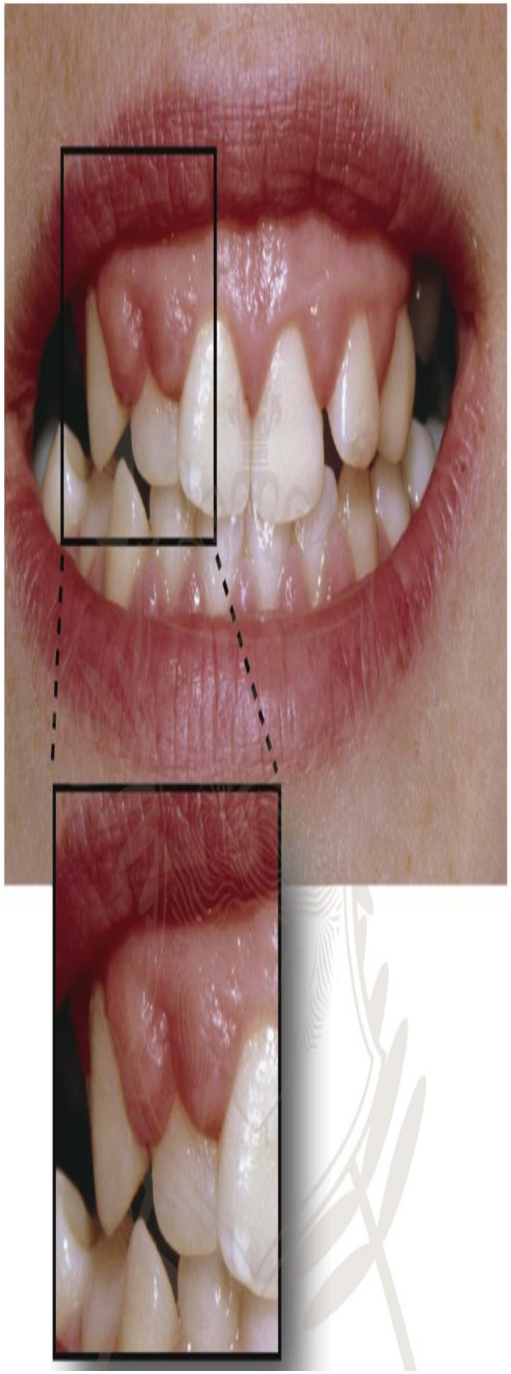
7. Hirsutism and acne due to increased androgen secretion

8. Osteomalacia with hypocalcemia

- occurs with chronic use (it interferes with vitamin D hydroxylation and reduces G.I. absorption of calcium).

9. Inhibit insulin release (hyperglycemia)

10. Neuropathies due to folate deficiency



HOW TO REMEMBER *SIDE EFFECTS OF PHENYTOIN*

IN 2 MINS

H	HIRSUTISM
O	OSTEOMALACIA
T	TERATOGENICITY
M	MEGALOBLASTIC ANEMIA
A	ARRHYTHMIA (at toxic doses)
I	INHIBITS INSULIN RELEASE
L	LYMPHADENOPATHY
G	GUM HYPERTROPHY
A	ATAXIA (at toxic doses)
N	NYSTAGMUS (at toxic doses)
D	DIPLOPIA (at toxic doses)
K	VITAMIN K DEFICIENCY

FETAL HYDANTOIN SYNDROME

- Cleft Lip
- Cleft Palate
- Microcephaly
- Hypoplastic phalanges

Drug interactions of phenytoin

- Displacement of phenytoin from plasma proteins: phenylbutazone, oral anticoagulants & sulfonamides.
- Inhibition of phenytoin metabolism by chloramphenicol & valproic acid.
- Phenytoin metabolism is enhanced by enzyme inducers: carbamazepine and phenobarbitone.
- Phenytoin (enzyme inducer) can increase the metabolism of warfarin, steroids.

Precautions

- Serum level monitoring is essential.
- Oral hygiene (frequent brushing, gum massage).
- Vit D and folate supplements should be given when necessary.

II- Carbamazepine and oxcarbamazepine (TCA related)

- **Pharmacokinetic:**

A: Following oral absorption

D: it enters the brain rapidly, cross placenta, bound to plasma protein

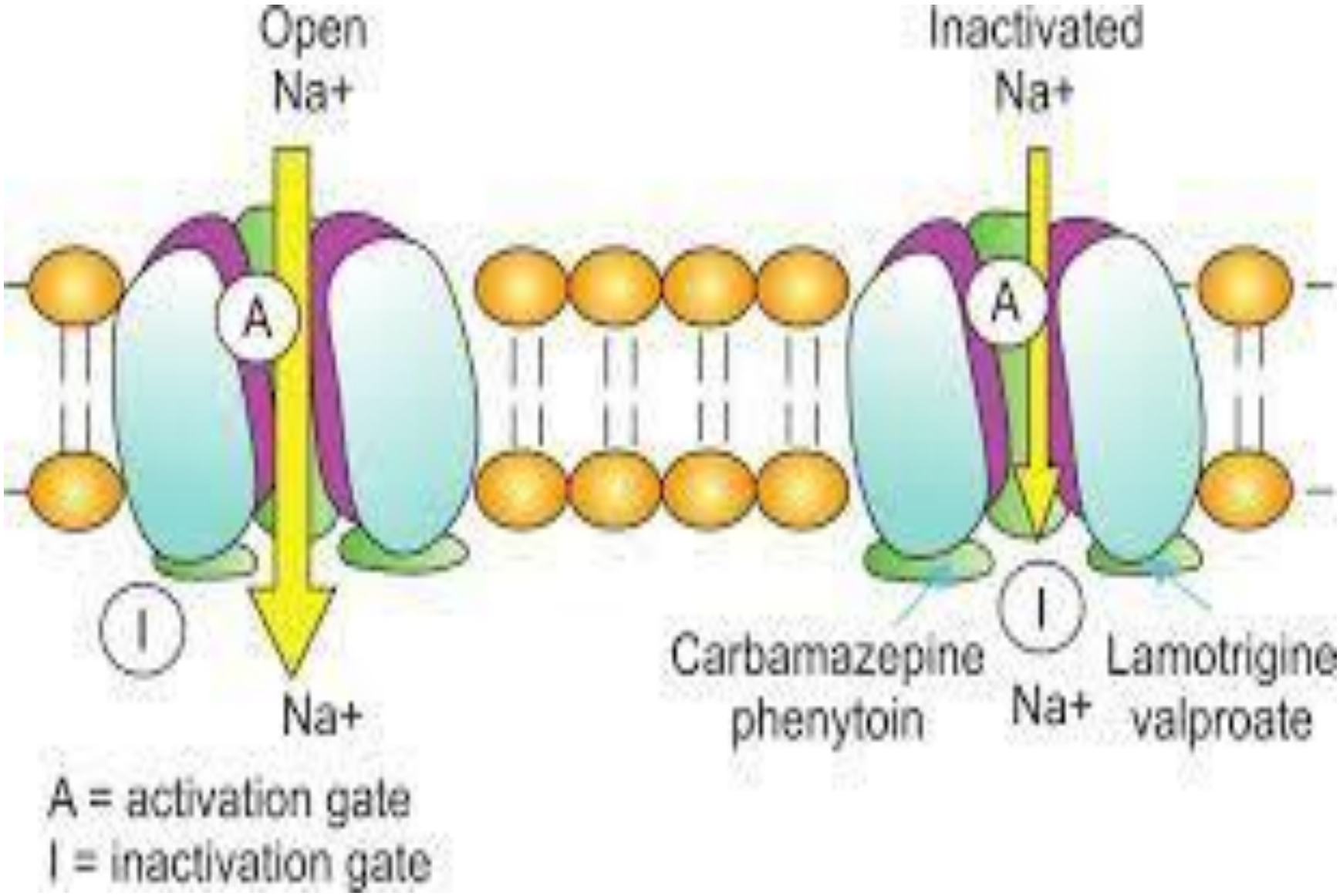
M: It induces hepatic microsomal enzymes.

Its half life decreases with chronic administration due to auto- induction

- The enhanced activity of liver microsomal enzymes also increases metabolism of many other drugs including anti-epileptics

- **Mechanism of action:**

It **blocks Na+ channels** and so reduces the propagation of abnormal impulses in the brain.


Open
Na+
Inactivated
Na+
A
A
I
I
Na+
Na+
Carbamazepine
phenytoin
Lamotrigine
valproate
A = activation gate
I = inactivation gate

Therapeutic uses

1. Focal seizures.

2. Trigeminal neuralgia.

3. Cerebral or nephrogenic diabetes insipidus

Side effects

1- C.N.S: Nustagmus, Diplopia, Ataxia & drowsiness.

2 .Liver dysfunction

3. Blood: Aplastic anemia, agranulocytosis (cause bone marrow depression).

4- Teratogenicity: craniofacial anomalies and spina bifida

5. G.I.T: nausea & vomiting.

6. Allergy: rash & photosensitivity.

7. Hyponatremia, water toxicity due to ↑ ADH effects.

8- Not used in treatment of absence seizures

Oxcarbazepine: prodrug convert to active metabolite

It is anticonvulsant. C.N.S. toxicities are similar to that of carbamazepine.

Lesser hepatic enzyme inducer

There are no reports of hepatic failure or bone marrow abnormality

III- Valproic acid, valproate and divalproex

- **Pharmacokinetics:**
  - Well absorbed orally.
  - 90% bound to plasma proteins.
  - Metabolized in the liver to toxic metabolites.
- **Mechanism of action:**
- It acts by increasing GABA concentrations in synaptic regions through:

-Inhibition of ***GABA transaminase*** (enzyme that breaks GABA) or

-Inhibition of ***GABA reuptake*** by nerve endings.

- It blocks Na+ channels & T-Ca+ channels.

Therapeutic uses:

1. **Broad** spectrum antiepileptic:

effective in generalized epilepsy & focal seizures but it is not the drug of choice (**sedation** & **hepatotoxicity**).

2. focal seizures **divalproex**

3. Absence epilepsy. **divalproex**

4. Febrile convulsion.

5. Myoclonus and tonic -clonic **divalproex**

6. Prophylaxis of migraine

Side effects:

1. CNS: N,A,D
2. liver: Hepatotoxicity.
3. Teratogenic: more increased incidence of spina bifida of any antiepileptic. Decrease I.Q for child.

4- G.I.T: anorexia, nausea & vomiting.

5- Hair loss (alopecia)

Drug interactions:

- Valproic acid inhibits the metabolism of phenobarbitone, phenytoin and carbamazepine.
- It displaces phenytoin from plasma protein binding sites.

V- Barbiturates (Bb and benzodiazepine Bz)

- **Phenobarbitone:** it has selective anticonvulsant activity & it may act through **potentiating the inhibitory pathway (GABA).**
- **Diazepam, Clonazepam & Lorazepam** : drug of choice for treatment of status epilepticus (rapid onset).

IV- Ethosuximide (LEAST TOXIC ANTIEPILEPTIC)

- **Pharmacokinetics**:
- Well absorbed orally.
- Not bound to plasma protein.
- 75% are metabolized.
- 25% are excreted unchanged.
- **Mechanism of action:** It blocks voltage-gated **T-Ca++ channels.**
- **Therapeutic uses:** It is the drug of first choice in **absence** seizures

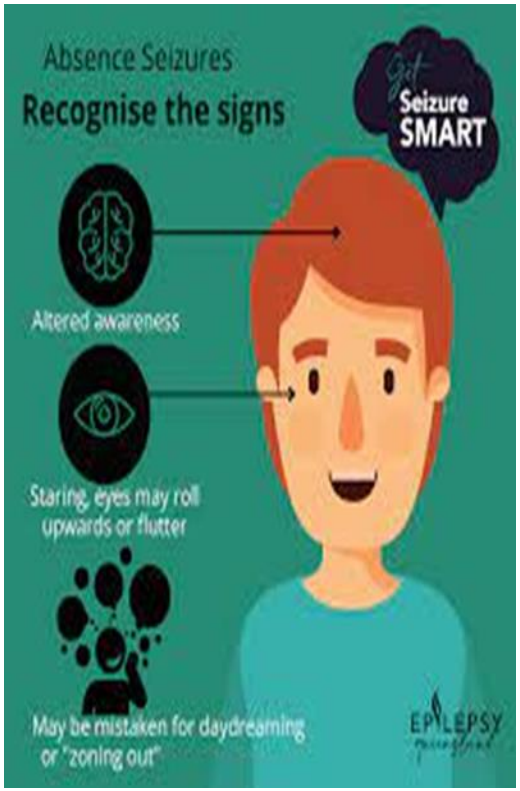
- **Side effects:**

1.G.I.T: nausea, vomiting & diarrhea

2.Allergy: skin rash & urticaria.

Absence Seizure

involves sudden lapse in consciousness and staring blankly into space, the episodes last less than 15 seconds



- Newer antiepileptic drugs (2ND generation)

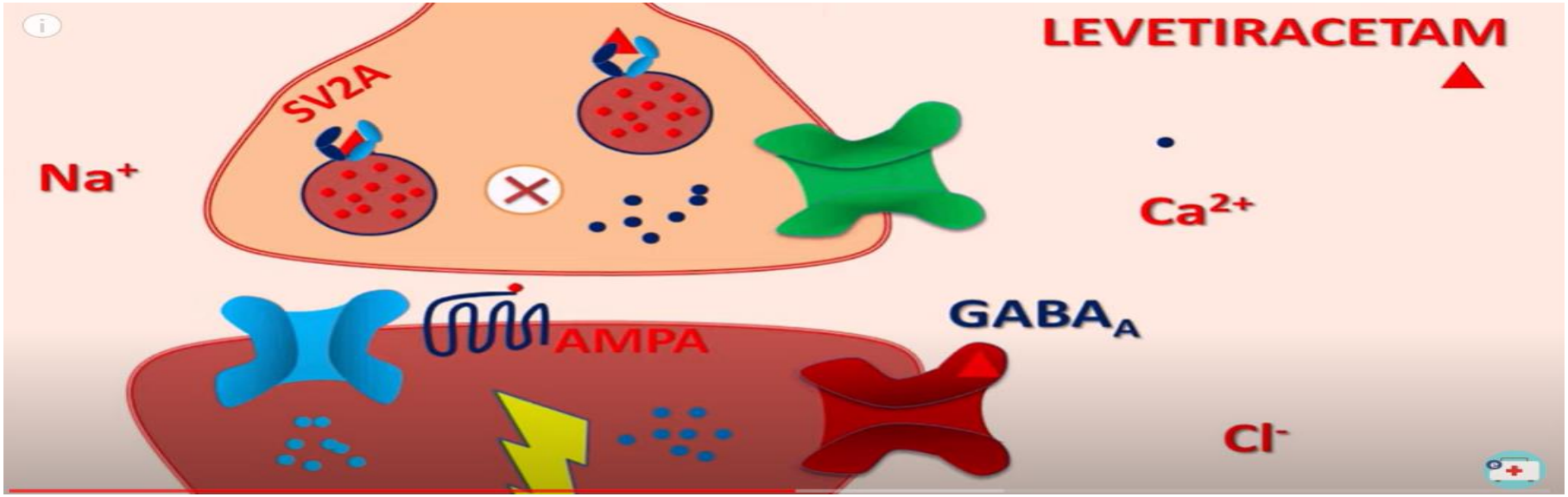
- All are used as add-on therapy in **refractory** epilepsy.
- Some of them have proved efficacy as **monotherapy**

Lamotrigine	Topiramate	Zonisamide (Sulfa)
• blocks Na & Ca++ channels. • used in **all type of epilepsy except status epileptics** • Side effects: dizziness, headache & ataxia, Stevens Johnson syndrome	• blocks Na & Ca++ channels. • Bind glutamate receptor • Used in: focal, generalized epilepsy and absence seizures • Side effects: impaired concentration, diplopia, weight loss & kidney stones	• Blocks Na+ & Ca++ channels. • Used in: focal, generalized epilepsy and absence seizures Side effect: kidney stones and oligohidrosis.

Gabapentin	Vigabatrine	Tiagabine	Pregabalin
• Enhance release of GABA. • They interfere with voltage-dependent Ca++ channels Uses: • Migraine and **neuropathic pain** **(post-herpetic neuralgia and diabetic neuropathy)**. • Approved as adjunct therapy for focal convulsions Side effects: dizziness, headache & ataxia	• It is irreversible inhibitor of GABA transaminase, increasing concentration of GABA. • Used in grand mal and focal seizures(refractory) • Side effects: sedation, dizziness & behavioral changes, **irreversible vision affection**	• It blocks GABA uptake (Transporter) into presynaptic neurons. • Used in: focal seizures • Side effect: dizziness & GI upset.	• They interfere with voltage-dependent Ca++ channels • INHIBIT excitatory transmitter release • Used in: focal seizures Side effects: dizziness, headache & ataxia

Levetiracetam and brivaracetam

- Modifies the release of glutamate and GABA by binding to synaptic vesicle protein(SV2A).
- **Used in: broad spectrum antiepileptic used in all types of epilepsy except status**
- **Side effects:** dizziness & sleep disturbances, behavioral changes.



Felbamate

- **Mechanism of action :** It blocks Na+ & Ca++ channels & competes with glycine cofactor at NMDA receptors.
- **Side effects:** liver and bone marrow toxicities, so it is reserved for use in refractory epilepsy.

Seizure Type	Effective Drugs
Partial—simple or complex	Valproic acid, phenytoin, carbamazepine, lamotrigine
General—tonic-clonic	Valproic acid, phenytoin, carbamazepine, lamotrigine
General—absence	Ethosuximide, valproic acid
Status epilepticus	Lorazepam, diazepam, phenytoin, or fosphenytoin*


Thank You